REMARKS

The amendments made to the claims herein are made to focus on specific embodiments of the invention. No new matter is introduced into the application by means of these amendments.

The examiner issued a new ground of rejection in the outstanding Office Action. Specifically, the examiner has rejected all of the pending claims under 35 U.S.C. §112, first paragraph, on the basis that although the specification is enabling for the specific low range of cadmium to be administered to a human by the particular route employed in the claimed method, it does not reasonably provide enablement for the dose range of about 0.025 t0 2 mg/day administered to a human by any administration route in view of the teachings of *"Cadmium Oxide,"* EPA Chemical Profiles, and Nordberg, et al., IARC Scientific Publications 118:293-297 (1992). The examiner asserted that the former reference teaches that cadmium is a highly toxic compound and that the latter reference indicates that the administration of cadmium can be unpredictable, especially with regard to dosage range and route of administration. This rejection is traversed.

Applicant now has focused the pending claims of the application on administration of cadmium by oral and parenteral means. As the examiner has noted, the application contains an

example (Experiment D of Example 3) which illustrates the oral administration of 1 mg of cadmium daily to three adult human males over a period of 6 weeks. Enclosed with this Amendment is a Declaration Pursuant to 37 C.F.R. § 1.132, by the Applicant[1], which, in relevant part, describes a second experiment in which 2 mg of cadmium were administered orally to an adult human male for a period of 9 weeks. The results of the study are summarized in the declaration. This additional study shows that cadmium can be orally administered safely for a prolonged period of time at the maximum dosage range set forth in the pending claims with no resultant evidence of toxicity.

The declaration further discusses the results of a series of toxicity studies in which cadmium salts were orally administered to rhesus monkeys. Rhesus monkeys are a good animal model for humans with regard to cadmium toxicity because humans and rhesus monkeys metabolize cadmium similarly (Nomiyama et al., *Environ. Health Perspect.* 28:223-243 (1979). As explained in Dr. Woods' declaration, doses of cadmium administered to the monkeys in these reported studies which were comparable to a human equivalent dose of 2 mg/day cadmium were found repeatedly to be non-toxic and safe. For example, the authors reported that

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[1]An unexecuted copy of the declaration is submitted with this Amendment. The executed copy will be submitted promptly.

monkeys who received the human equivalent of 1.68 mg/day for one month, followed by 2.52 mg/day for 13 months and then 3.36 mg/day for the next 16 months showed no adverse effects. The results of this study provide further evidence that the doses set forth in the present application will not cause toxicity in humans.

As Dr. Woods further explains in his declaration, an oral dose of about 0.5 mg/day to about 2 mg/day is comparable to a parenteral dose of about 0.025 mg/day to about 0.1 mg/day. When cadmium is administered orally, about 95% of the cadmium passes through the gastro-intestinal system and is not absorbed into the rest of the body; only about 5% is therapeutic. When a dose is administered parenterally, such as intravenously, essentially all of the cadmium can be absorbed and available as a therapeutic. Thus, parenteral doses that are about 5% of the oral doses are comparable to the oral doses and are suitable and effective.

The pending claims remain rejected under 35 U.S.C. §102(b) as anticipated by Jacobson et al. The examiner asserted that Jacobson et al. disclose the administration of 20 trace elements, including cadmium, to humans to correct negative balances of the elements. The examiner further asserted that the amounts of cadmium administered daily were 50-60 µg (0.05-0.06 mg) or 5-68 µg (0.005-0.068 mg), which was within the range of the present invention. This rejection again is traversed.

The presently claimed invention is directed to a method of treating a person suffering from deficient levels of cadmium in his body fluids and tissues by administering to the person a series of daily doses of cadmium. As amended, the claims are directed to parenteral administration at dose levels of about 0.025 mg to about 0.1 mg per day (equivalent to a dose level of about 25 - 100 µg per day) or oral administration at dose levels of about 0.5 mg to about 2 mg per day (equivalent to a dose level of about 500 - 2000 µg per day). This invention is not taught or suggested by Jacobson et al.

Jacobson et al. report a 5 day study in which they administered a number of trace elements parenterally to four adult human males. The amount of cadmium administered ranged from 1.2 to 4.0 µg per day. See Table 5, page 114. This dosage amount is far below the amount of cadmium to be administered parenterally in accordance with the present invention. As noted above, the present claims require a concentration of 0.025 - 0.1 mg be administered parenterally per day, which is the equivalent of 25-100 µg per day. The amounts of cadmium administered in the Jacobson study were so small that three of the four patients excreted higher amounts of cadmium in their urine than had been administered.

The examiner's statement that the paper teaches the administration of 0.05-0.06 mg of cadmium is a mis-reading of the reference. The passage the examiner cited from page 121 does not relate to the amount of cadmium parenterally administered to the subjects in this study. Rather, the reference to 0.05 - 0.06 mg of cadmium is a reference to the average amount of cadmium typically ingested per day as a natural part of one's typical food intake; the authors then note that the food in ordinary hospital diets provide from 0.005 - 0.068 mg of cadmium daily. Applicant notes in the background of his application that small amounts of cadmium are ingested as a matter of course in various foods and then teaches that oftentimes, especially for those who consume typical Western diets, the amounts ingested are insufficient, such that cadmium must actually be administered to humans to minimize or eliminate the cadmium deficiency that has developed as a result of the inadequate intake of cadmium in food. Applicants teach the administration of cadmium, supplemental to that typically obtained in food, to prevent or treat cadmium deficiencies in body fluids and tissues. One of ordinary skill in the art would not consider eating food which inherently contain small amounts of cadmium to be the "administration" of cadmium as taught and claimed in the present application. Furthermore, the amounts of cadmium noted to be

found in food is far less than the about 0.5 mg - about 2 mg to be orally administered in accordance with the oral administration embodiment of the claimed invention. Thus, the amounts of cadmium parenterally administered in the study reported in this reference are significantly below the amounts to be administered parenterally in accordance with the present invention, and the amounts of cadmium orally ingested reported in this reference are far below the amounts of cadmium to be orally administered in accordance with this invention.

The cited reference further is deficient in that there is no indication that the four men to whom the parenteral nutritional supplement was administered suffered from a cadmium deficiency. Even if they did, the amounts of cadmium given them, from 0.0012 mg - 0.004 mg, was far less than the amount required by the pending claims and would not be sufficient to treat a cadmium deficiency, which, as indicated in the present application, can be at least 15% below normal physiological levels. Jacobson et al. certainly do not teach or suggest that greater amounts could or should be given. The largest amount of cadmium they administered, 0.004 mg, is only <u>one-sixth</u> the minimum amount taught and claimed by the Applicant. Moreover, there is no indication in the Jacobson et al. paper that the authors are advocating the administration of cadmium; the discussion of

dietary cadmium is part of a larger discussion of trace elements not established as essential for man or animals, and they note that cadmium "has not been attributed any special role in the living cell." Indeed, the very small amounts of cadmium administered appear to have been present unintentionally. Table 1 of the paper provides the composition of the parenteral nutrition solutions administered during the study. Different solutions were administered at different times of the day. The solutions were (1) a carbohydrate solution and a soluble vitamin mixture, (2) an amino acid solution and an electrolyte solution, (3) a combination of a fat emulsion, lipovit emulsion and heparin, and (4) a carbohydrate solution. The components of the different solutions are listed in subsequent tables, none of which include cadmium as a component. In the Abstract, the authors note that the "intended intravenous supply of trace elements [presumably those listed in the initial tables of the paper] corresponded approximately to the analyzed supply," but that "all other trace elements determined were found to be unintentionally administered in small amounts."

At the end of their paper the authors discuss recommendations for trace element dosage, per 24 hours, in total parenteral nutrition for adults. None of the recommendations, provided in Table 6, include cadmium as an element to be

administered. The authors state that the US National Research Council recommended that only iodine, iron and zinc be included regularly in the diet and that other trace elements are supposed to be adequate in the variety of common foods eaten. The authors suggest that on the basis of their results, trace element solutions used in total parenteral nutrition might be improved if they provided more zinc and less iron, to cover the basic requirements more appropriately. "Otherwise, the quantities of infusion solutions used in the total parenteral nutrition studied seem to supply adequate basic amounts of trace elements, essential for human nutrition" (from the paragraph bridging pages 124-125). From this discussion, one would be left believing that, at best, cadmium should be administered parenterally only at doses not to exceed 4 μg, and that perhaps cadmium need not be administered at all. There is no realization that persons can suffer from a cadmium deficiency or that relatively large amounts of cadmium can or should be administered parenterally or orally to such people to treat such deficiencies. If, indeed, any of the patients in the study had a cadmium deficiency, they certainly did not receive treatment for that deficiency.

In responding to the Applicant's previous arguments regarding the Jacobson reference, the examiner asserted that the

reference "clearly teaches that the amount of Cd is known in the art by citing several prior art [references] (see page 122 therein)." Applicant respectfully submits that neither page 122 nor any other page of the reference teaches the administration of cadmium in the amounts taught and claimed by Applicant. This page of the reference does cite several references that mention the amounts of cadmium found in urine or serum, but none of these statements makes any reference to cadmium administration--by any route or in any dose.

In view of the deficiencies of the Jacobson et al. reference, the reference does not anticipate the claims of this application.

Claims 21-22 and 25 remain rejected under 35 U.S.C. § 103(a) as being obvious over the teachings of the Jacobson et al. paper discussed above or U.S. Patent 4,225,592 issued to Lakatos (hereinafter referred to as the '592 patent). The examiner stated that the relevance of the Jacobson patent had been discussed in the previous rejection based upon that reference and that the '592 patent teaches that it is well-known to administer trace elements such as cadmium as nutrition and that the teachings regarding the administration of such trace elements in this reference are based on several cited prior art references. She noted that the prior art does not expressly disclose the

particular unbalanced levels of cadmium in humans or particular cadmium salts to be administered. She asserted, however, that it would have been obvious to determine the level of cadmium and the particular salt to be administered so as to increase the concentration of cadmium in body fluids and tissues and correct a cadmium imbalance. This rejection is traversed.

The deficiencies of the Jacobson et al. paper have been discussed at length above, and those discussions are equally applicable to this rejection. The Jacobson et al. paper discloses the administration of small amounts of cadmium over a very short time period (five days). There is no indication that the persons to whom Jacobson et al. administered the cadmium (and other trace elements) were cadmium deficient, and the amounts of cadmium administered are significantly below the amounts set forth in the present claims and are not sufficient to treat a cadmium deficiency. This reference thus does not render obvious the invention of claims 21, 22 or 25.

The teachings of the '592 patent also do not render obvious claims 21, 22 or 25. The focus of the '592 patent, the administration of complexes of oligo- and polygalacturonic acid formed with selected essential metal ions, none of which is cadmium, is of no relevance to the presently claimed invention, and the examiner has not asserted otherwise. The examiner's

focus on this reference is on a discussion of trace elements in column 9 of the patent. The examiner has asserted that the paragraph extending from lines 21-46 of this column teaches that it is well-known to administer cadmium and other trace elements to humans as nutrition. Applicant respectfully submits that the examiner has mis-read the discussion in the cited paragraph. What the paragraph actually provides is that the a person's ability to absorb magnesium and trace metals such as iron, zinc and copper and chromium significantly decreases, and the secretion of these elements increases, with age, and that as a result, disorders such as anemia, athero- and arteriosclerosis, diabetes, cardiovascular diseases, nephrolithiasis and ulcus emerge. The paragraph further states that in response to this, numerous vitamins and preparations containing essential elements are sold as geriatric preparations, and a preparation which makes possible the simple and efficient administration of these trace elements would be desirable.

There is no mention in this discussion regarding the administration of cadmium. The only reference to cadmium is in the title of one of the papers cited as authority for the statement that the absorption of zinc and copper decreases with age. To support this statement, the patentees cited M. Anke and H.J. Schneider, "Zinc, Cadmium and Copper Metabolism in Men;"

Arch. Exp. Veterinaermed., 25:805-809 (1971) (column 9, lines 27-29 of the '592 patent). Applicant submitted a copy of this paper, along with an English translation hereof, as Attachment A to the Amendment filed in June, 2004. A review of the translation shows that the paper does not teach or suggest that cadmium should be administered to humans who are suffering from a cadmium deficiency. The paper simply reports, as the title of the paper indicates, on the metabolism of zinc, cadmium and copper in humans. The authors looked at differences in metabolism between men and women and at the effects of age on metabolism. In pertinent part, this paper provides that cadmium is stored in the liver and kidneys as people age, and that the kidneys of men have significantly more cadmium than the kidneys of women. The authors also reported that cadmium levels in kidneys for both men and women tended to decrease significantly after the age of 70. They also found that there was variation in the concentration of zinc in kidneys and that this was determined by cadmium rather than by age. They stated (page 5 of the translation) that cadmium has a "metabolism-stressing" role and that their data showed the "toxic effects" of cadmium.

The authors further asserted that the kidneys and liver of persons who die from cardiac insufficiency, inflammatory pulmonary disease and malignant tumors contained a definitely

established greater amount of cadmium; persons dying from infarction had a significantly lower concentration of cadmium than that of other patients. The authors asserted that cadmium may play a role in the occurrence of cardiac insufficiency, inflammatory pulmonary diseases and carcinoma. There is no suggestion that humans can suffer from a cadmium deficiency, much less that it would be desirable to treat such a deficiency by the administration of cadmium, and certainly there is no suggestion of the oral or parenteral administration of cadmium in the doses set forth in the claims. As there is no discussion of cadmium deficiencies, there is no recognition that persons can suffer from a deficiency of 15-20% as required by claims 21 and 22, respectively, or of specific cadmium salts to be administered as set forth in claim 25.

As noted above, the paper by Anke and Schneider is the only reference to cadmium in the '592 patent. The '592 patent, therefore, does not suggest the presently claimed invention and does not render obvious claims 21, 22 or 25.

Applicant respectfully submits that in view of the amendments and arguments presented herein, the invention claimed in the present application is in condition for allowance.

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